FOLLOW-ON DOCUMENT INDEX SHEET

CFILE Request for Corrected Filing Receipt	PEFRSEQ Pre-Exam Formalities Sequence Reply	ACPA Continuing Prosecution Application
IFEE Issue Fee Transmittal PTOL 85 B	CRFD Computer Readable Form Defective	AF/D Affidavit or Exhibit Received
PEFR Pre-Exam Formalities Response	CRFE Computer Readable Form 'ENTERED'	AP.B Appeal Brief
PEFRREISS Pre-Exam Formalities Reissue Response	CRFL CRF Transfer Request	C680 Request for Corrected Notice/Allowance
A... Amendment Including Elections	CRFS Computer Readable Form Statement	COCIN Papers filed re: Certificate of Corrections
A.NA Amendment after Notice of Allowance	SEQLIST Sequence Listing	EABN Request for Express Abandonment
A.NE After Final Amendment	EARLYPUB Request for Early Publication	IRFND Refund Request
A.PE Preliminary Amendment	PGEA Req Express Aband to Avoid Publication	L_RIN Any Incoming L&R
REM Applicant Remarks in Amendment	PGA9 Req for Corrected Pat App Publication	N/AP Notice of Appeal
ELC. Response to Election/Restriction	PGREF Req for Refund of Publication Fee Paid	N417 Copy of EFS Receipt Acknowledgement
RCEX Request for Continued Examination	PGPUB DRAWINGS Box PG Pub Drawings	PROTEST Protest Documents Filed by 3rd Party
SPEC Specification	RESC Rescind Non-Publication Request	PROTRANS Translation of Provisional in Nonprov App
CLM Claim	XT/ Extension of Time filed separate	C.AD Change of Address
ABST Abstract	371P PCT Papers in a 371P Application	PA.. Change in Power of Attorney
DRW Drawings	IDS IDS including 1449	PC/I Power to Make Copies or to Inspect
OATH Oath or Declaration	FOR Foreign Reference	PET. Petition
ADS Application Data Sheet	NPL Non-Patent Literature	PET.WDISS Petition to Withdraw from Issue
APPENDIX Appendix	FRPR Foreign Priority Papers	PETDEC Petition Decision
ARTIFACT Artifact	DIST Terminal Disclaimer filed	LET. Miscellaneous Incoming Letter
COMPUTER Computer Program Listing	L_RACK L&R Access Acknowledgement	IMIS Miscellaneous Internal Document
SPEC NO Specification Not in English	ROCKET Request for Expedited (Rocket Docket)	RETMAIL. Mail Returned by Post Office
136A Blanket authorization to charge fees		

DOCKET NO.: JANS-0027 **PATENT**

	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	FEE	RATE	FEE
☒ APPEAL BRIEF FEE	$165	$	$330	$330.00
☐ ONE MONTH EXTENSION OF TIME	$55	$	$110	$0
☐ TWO MONTH EXTENSION OF TIME	$210	$	$420	$0
☐ THREE MONTH EXTENSION OF TIME	$475	$	$950	$0
☐ FOUR MONTH EXTENSION OF TIME	$740	$	$1480	$0
☐ FIVE MONTH EXTENSION OF TIME	$1005	$	$2010	$0
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TOTAL FEE DUE		$0		$330.00

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.

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☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

Date: September 3, 2004

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DOCKET NO.: JANS-0027 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Frans Eduard Janssens, *et al***
Serial No.: **10/030,202**
Filing Date: **December 27, 2001**
Confirmation No.: **9001**
Group Art Unit: **1624**
Examiner: **Kahsay Habte**

For: **RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS**

EXPRESS MAIL LABEL NO: EL 999282785 US
DATE OF DEPOSIT: September 3, 2004

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANTS' BRIEF PURSUANT TO 37 C.F.R. § 1.192

This brief is filed in support of Appellants' appeal from the rejections of claims of claims 1 to 4, 10, 13, 15, and 18 to 21 dated March 15, 2004. A Notice of Appeal was filed on July 8, 2004.

1. REAL PARTY IN INTEREST

Based on information supplied by Appellants and to the best of the undersigned's knowledge, the real party in interest in the above-identified patent application is Janssen Pharmaceutica N.V., a subsidiary of Johnson & Johnson.

2. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Appellants, its legal representative, or the assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

3. STATUS OF CLAIMS

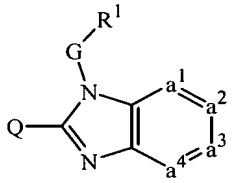
Claims 1 to 4, 6, 8 to 10, 13 to 15, and 18 to 21 are pending in this application. Claims 1 to 4, 10 to 13, 15, and 18 to 21 stand rejected. Claims 6, 8, and 14 stand objected to because they depend from rejected base claims but would be otherwise allowable if rewritten in independent form. Claim 9 is allowed. Appellants are appealing the rejection of claims 1 to 4, 10, 13, 15, and 18 to 21. Pending claims 1 to 4, 6, 8 to 10, 13 to 15, and 18 to 21 appear in Appendix A.

4. STATUS OF AMENDMENTS

The Amendment filed on May 27, 2004 was not entered.

5. SUMMARY OF INVENTION

In a first aspect, the present invention is directed to methods of manufacturing a medicament for the treatment of respiratory syncytial viral infections, comprising the step of admixing a pharmaceutically acceptable carrier and a compound of the general formula (I):



(I)

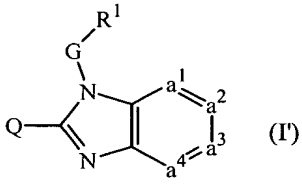
or an addition salt or stereochemically isomeric form thereof;

wherein $-a^1=a^2-a^3=a^4-$ represents a radical of formula

$$-CH=CH-CH=CH- \quad (a\text{-}1).$$

See claim 1 and the specification, page 2, line 6 to page 4, line 9.

In a second aspect, the present invention is directed to compounds of the general formula (I'):



(I')

an addition salt or stereochemically isomeric form thereof,

wherein $-a^1=a^2-a^3=a^4-$ represents a radical of formula

$$-CH=CH-CH=CH- \quad (a\text{-}1).$$

See claims 2 to 4 and the specification, page 4, line 17 to page 6, line 19. The compounds of formula (I') differ from the compounds of formula (I) useful in the method of claim 1 in that certain compounds are excluded by proviso from the genus of the compounds of formula(I') (where G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl).

In a third aspect, the present invention is directed to methods of treating a respiratory syncytial viral infection, comprising the step of administering a therapeutically effective amount of the compound of formula (I'). See claim 10 and the specification, page 4, lines 11 to 16.

In a fourth aspect, the present invention is directed to pharmaceutical compositions, comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of the compound of formula (I'). See claim 13 and the specification, page 44, line 32 to page 47, line 8.

In a fifth aspect, the present invention is directed to processes of preparing a compound of formula (I') comprising at least one step selected from the group consisting of:

a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III);

b) deprotecting an intermediate of formula (IV);

c) deprotecting and reducing an intermediate of formula (IV-a);

d) deprotecting an intermediate of formula (V);

e) deprotecting an intermediate of formula (VI);

f) deprotecting an intermediate of formula (VII) or (VIII);

g) amination of an intermediate of formula (IX);

h) reducing an intermediate of formula (X);

i) reducing an intermediate of formula (X-a);

j) amination of an intermediate of formula (XI);

k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia;

l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)

m) reducing an intermediate of formula (XV);

n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b);

o) amination of an intermediate of formula (XVII); and

p) amination of an intermediate of formula (XIX)

See claims 15 and 18 to 21 and the specification, page 18, line 32 to page 44, line 10.

6. ISSUE

The only issue in this appeal is whether claims 1 to 4, 10, 13, 15, and 18 to 21 are obvious under 35 U.S.C. § 103(a) in view of US-A-5,360,807.

7. GROUPING OF CLAIMS

The rejected claims do not stand or fall together. Five groups of claims are believed to provide separate embodiments of this invention, and should be considered independently of one another for the purpose of this appeal:

(1) Claim 1 is directed to methods of manufacturing a medicament for the treatment of respiratory syncytial viral infections;

(2) Claims 2 to 4 are directed to compounds of the general formula (I');

(3) Claim 10 is directed to methods of treating a respiratory syncytial viral infection;

(4) Claim 13 is directed to pharmaceutical compositions;

(5) Claims 15 and 18 to 21 are directed to processes of preparing a compound of formula (I').

8. ARGUMENT

CLAIMS 1 TO 4, 10, 13, 15, AND 18 TO 21ARE NOT RENDERED OBVIOUS BY THE ANTIALLERGY PRIOR ART UNDER 35 U.S.C. § 103(a)

Appellants respectfully submit that claims 1 to 4, 10 to 11, 13, and 15 to 21 are not obvious under 35 U.S.C. § 103(a) over US-A-5,360,807. It is respectfully submitted that there is no motivation to modify the cited reference to achieve appellants' claimed invention because US-A-5,360,807 is directed to antiallergic and antihistamine compounds whereas appellants' claimed novel compounds, compositions, and methods of employing novel and known compounds for the treatment of respiratory syncytial viral infections.

Obviousness is a question of law based on underlying factual determinations. See *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). In determining whether the claimed subject matter would have been obvious to those of ordinary skill, the following four factual inquiries must be undertaken:

- a consideration of the scope and content of the pertinent prior art;
- a determination of the level of ordinary skill in the pertinent art at the time that the invention was made;
- an identification of the differences between the pertinent prior art and the claims at issue; and
- the extent of any proffered objective indicia of nonobviousness.

Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). An analysis of obviousness of a claimed combination must include consideration of the results achieved by that combination. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

The scope of the prior art includes art that is "reasonably pertinent to the particular problem with which the invention was involved." *Stratoflex, Inc., v. Aeroquip Corp.*, 713

F.2d 1530, 1535 (Fed. Cir. 1983). In order to prevent hindsight-based obviousness analysis, the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to achieve the claimed invention. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998).

It is respectfully submitted that it has not been established that the invention is *prima facie* obvious. To establish a proper *prima facie* rejection, the following elements must be shown:

(1) the reference(s) is (are) available as prior art against the claimed invention;

(2) the motivation (explicit or implicit) provided by the reference(s) that would have rendered the claimed invention obvious to one of ordinary skill in the art at the time of the invention;

(3) a reasonable expectation of success;

(4) the basis for concluding that the claimed invention would have been obvious to do, not merely obvious to try; and

(5) the reference(s) teach(es) the claimed invention as a whole.

Appellants submit that elements 2, 3, 4 and 5 have not been established. Hence, a *prima facie* obviousness rejection is improper. *In re Grabiak*, 769 F.2d 729, 733, 226 U.S.P.Q. 870, 873 (Fed. Cir. 1983).

In the office action, it is alleged that some of the compounds of the invention are structural homologues of the compounds disclosed in US-A-5,360,807. It is further alleged that a skilled artisan would be motivated to modify the reference to achieve the presently claimed invention because such compounds "would be expected to possess similar utilities." Appellants disagree that the cited reference and the claimed invention "possess similar utilities." US-A-5,360,807 discloses the use of its compounds in methods of treating warm-blooded animals suffering from *allergic diseases*, whereas the claimed invention is directed to compounds, compositions, and methods useful for treating *respiratory syncytial viral*

infections. It is submitted that allergic diseases and respiratory syncytial viral infections are different:

> An ***allergy*** is a state of hypersensitivity induced by exposure to a particular antigen (allergen) resulting in harmful immunologic reactions on subsequent exposures, the term is usually used to refer to hypersensitivity to an environmental antigen (atopic allergy or contact dermatitis) or to drug allergy.
> *On-line Medical Dictionary, Academic Medical Publishing & CancerWEB (enclosed)*

> A ***respiratory syncytial viral infection*** is an infection (an invasion and multiplication of microorganisms in body tissues) caused by the RNA virus (a member of the *Paramyxoviridae* family). The virus is a major pathogen in the upper and lower respiratory tract in both infants and younger children. Respiratory syncytial virus manifestations include bronchiolitis, pneumonia and croup.
> *On-line Medical Dictionary, Academic Medical Publishing & CancerWEB (enclosed)*

Furthermore, no connection has been established between the treatment of allergic diseases and the treatment of respiratory syncytial viral infections, a burden that must be carried by the Office not the appellants to establish *prima facie* obviousness (as incorrectly stated in the Office Action). It is respectfully submitted that a skilled artisan would have no expectation that the compounds of US-A-5,360,807, some of which may be structural homologues of the compounds of claimed invention, would be useful in methods of treating respiratory syncytial viral infections and thus would have no motivation to modify the reference, especially in a manner to achieve appellants' claimed compounds, compositions, and methods.

None of the compounds of claims 2 to 4 or compositions of claim 13 are disclosed in or suggested by US-A-5,360,807. It is respectfully submitted that the skilled artisan looking for new antiviral agents would not have been motivated to use the compounds or compositions disclosed by US-A-5,360,807 because the compounds and compositions disclosed therein are alleged as useful as antiallergic agents and there is no established link between antiallergic agents and antiviral agents. The Office advances that the compounds would be obvious to try – an improper standard to apply with respect to obviousness determinations. Furthermore, there is no reasonable expectation of success since there is no

established link between agents useful to treat allergies and those useful to treat viral infections.

Likewise, there is no disclosure, teaching, or suggestion in US-A-5,360,807 to use the compounds disclosed therein in a method of a medicament for the treatment of respiratory syncytial viral infections (claim 1 using compounds of formula (I)) or in a method of treating a respiratory syncytial viral infection (claim 10 using compounds of formula (I')). It is respectfully submitted that new, unobvious uses for compounds – even if the compounds are known (and appellants are not conceding that their compounds were known) -- are patentable. Clearly, this rule should apply to claims 1 and 10, since the use of the compounds of formula (I) and formula (I') as antiviral agents is not suggested by US-A-5,360,807.

Furthermore, there is no disclosure, teaching, or suggestion in US-A-5,360,807 to make the compounds of formula (I'), since these compounds are not disclosed, taught, or suggested by US-A-5,360,807.

Accordingly, appellants respectfully request withdrawal of the rejection of claims 1 to 4, 10, 13, 15, and 18 to 21 under 35 U.S.C. § 103(a) in view of US-A-5,360,807.

9. CONCLUSION

For the forgoing reasons, it is respectfully submitted that claims 1 to 4, 10, 11, 13, 15, and 18 to 21 are nonobvious with respect to the prior art. Appellants, therefore, request that this patent application be remanded to the Patent Office with an instruction to both withdraw the rejection of the claims under 35 U.S.C. § 103(a) and allow the appealed claims.

Date: September 3, 2004

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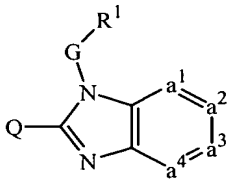
Facsimile: (215) 568-3439

APPENDIX A

1. A method of manufacturing a medicament for the treatment of respiratory syncytial viral infections, comprising the step of admixing a pharmaceutically acceptable carrier and a compound of formula



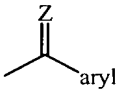
(I)

an addition salt or stereochemically isomeric form thereof,

wherein $-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

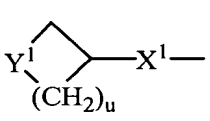
$-CH=CH-CH=CH-$ (a-1);

wherein each hydrogen atom in the radical (a-1) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula



wherein Z is O, CH-C(=O)-$NR^{5a}R^{5b}$, CH_2, CH-C_{1-6}alkyl, N-OH or N-O-C_{1-6}alkyl;

Q is a radical of formula



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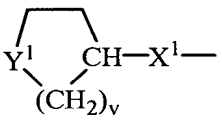
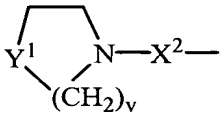


(b-5)

or,



(b-6)

;

wherein

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

u is 2 or 3;

v is 2; and

whereby each hydrogen atom in the carbocycles and the heterocycles defined in radicals (b-4), (b-5), and (b-6) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, and isothiazolyl; and each heterocycle may optionally be substituted with 1 or where possible more substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or

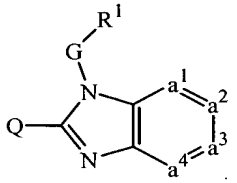
R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula -(CH_2)$_s$- wherein s is 4 or 5;

R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more-substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy; and

Het is pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl.

2. A compound of formula (I')



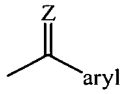
(I')

an addition salt or stereochemically isomeric form thereof,

wherein -a^1=a^2-a^3=a^4- represents a radical of formula

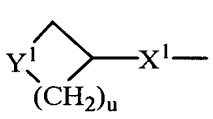
-CH=CH-CH=CH- (a-1);

wherein each hydrogen atom in the radicals (a-1) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

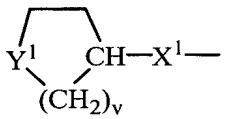


wherein Z is O, CH-C(=O)-$NR^{5a}R^{5b}$, CH_2, CH-C_{1-6}alkyl, N-OH or N-O-C_{1-6}alkyl;

Q is a radical of formula

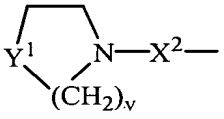


(b-4)



(b-5)

or,



(b-6) ;

wherein

Y^1 is a bivalent radical of formula –NR^2- or –CH(NR^2R^4)-;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

u is 2 or 3;

v is 2; and

whereby each hydrogen atom in the carbocycles and the heterocycles defined in radicals (b-4), (b-5), and (b-6) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, $HO(-CH_2-CH_2-O)_n$-, halo$(-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$-, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$- and mono-or di(C_{1-6}alkyl)amino$(-CH_2-CH_2-O)_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, formyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

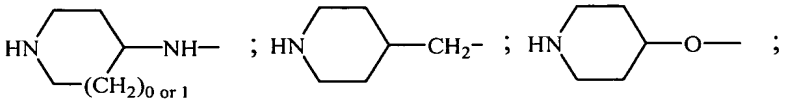
R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or

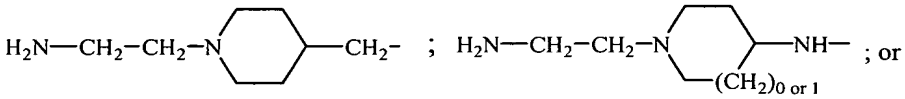
R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;

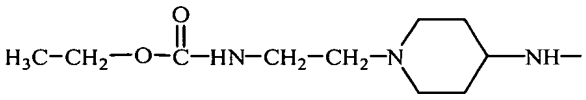
R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

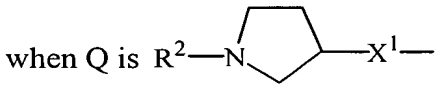
provided that when G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl, then Q is other than





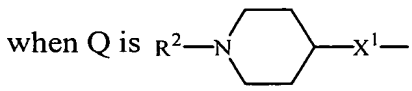


3. A compound as claimed in claim 2, wherein:



wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

4. A compound as claimed in claim 2, wherein:

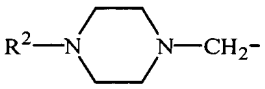


wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyridyl substituted

with 1 or 2 C_{1-6}alkyloxy, pyrazinyl, pyrrolyl, pyrrolyl substituted with C_{1-6}alkyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

5. ***(cancelled)***

6. A compound as claimed in claim 2, wherein:

when Q is 

then R^1 is other than pyridyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

7. ***(cancelled)***

8. A compound as claimed in claim 2, wherein the compound is:

(±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate;

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-1H-benzimidazol-1-yl]methyl-3-pyridinol;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(1,4-dimethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-ethoxyethoxy)-6-methyl-2-pyridinyl]methyl]-1H-benzimidazol-2-amine tetrahydrochloride dihydrate;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-chloro-1,4-dimethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(2-chloro-1,4-dimethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-methyl-1-[(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-aminopropyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-1H-benzimidazol-2-amine tetrahydrochloride trihydrate;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-1H-benzimidazol-2-amine;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-chloroethoxy)-6-methyl-2-pyridinyl]methyl]-1H-benzimidazol-2-amine trihydrochloride dihydrate;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[3-amino-2-pyridinyl)methyl]-1H-benzimidazol-2-amine tetrahydrochloride trihydrate;

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-4-methyl-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride;

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-chloro-4-methyl-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride 2-propanolate (1:1);

(±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-4-methyl-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol;

(±)-2-[[2-[[1-(2-aminopropyl)-4-piperidinyl]amino]-4-methyl-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride trihydrate;

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-7-methyl-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride dihydrate;

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-bromo-4-methyl-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride;

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate;

(±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-[(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

an addition salt or stereochemically isomeric form thereof.

9. A compound, wherein the compound is:

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-5-chloro-7-methyl-1H-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride tetrahydrate;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,4-dimethyl-5-oxazolyl)methyl]-1H-benzimidazol-2-amine;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,5-dimethyl-4-oxazolyl)methyl]-1H-benzimidazol-2-amine trihydrochloride monohydrate;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(5-methyl-3-isoxazolyl)methyl]-1H-benzimidazol-2-amine trihydrochloride monohydrate;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-5-oxazolyl)methyl]-1H-benzimidazol-2-amine monohydrate;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-5-oxazolyl)methyl]-1H-benzimidazol-2-amine trihydrochloride monohydrate;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-thiazolylmethyl)-1H-benzimidazol-2-amine;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]-1H-benzimidazol-2-amine trihydrochloride;

5-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino-1H-benzimidazol-1-yl]methyl-2-oxazolemethanol tetrahydrochloride dihydrate;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(3-methyl-5-isoxazolyl)methyl]-1H-benzimidazol-2-amine trihydrochloride monohydrate;

4-[[1-[[2-(dimethylamino)-4-thiazolyl]methyl]-1H-benzimidazol-2-yl]methyl]-1-piperidineethanamine tetrahydrochloride monohydrate 2-propanolate (1:1);

ethyl 5-[[2-[[1-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]-4-piperidinyl]amino]-1H-benzimidazol-1-yl]methyl]-2-methyl-4-oxazolecarboxylate;

4-[[1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-yl]methyl]-1-piperidineethanamine;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-3-furanyl)methyl]-1H-benzimidazol-2-amine;

1,1-dimethylethyl 4-[[1-[[3-[2-(dimethylamino)ethoxy]-6-methyl-2-pyridinyl]methyl]-1H-benzimidazol-2-yl]amino-1-piperidinecarboxylate;

ethyl 4-[[1-[(3-amino-2-pyridinyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinecarboxylate;

N-[1-(6-methyl-2-pyridinyl)-1H-benzimidazol-2-yl]-1-(3-pyridinylcarbonyl)-4-piperidinamine;

an addition salt or stereochemically isomeric form thereof.

10. A method of treating a respiratory syncytial viral infection, comprising the step of administering a therapeutically effective amount of said compound according to any one of claims 2 to 4, 6, 8 to 9.

11. ***(cancelled)***

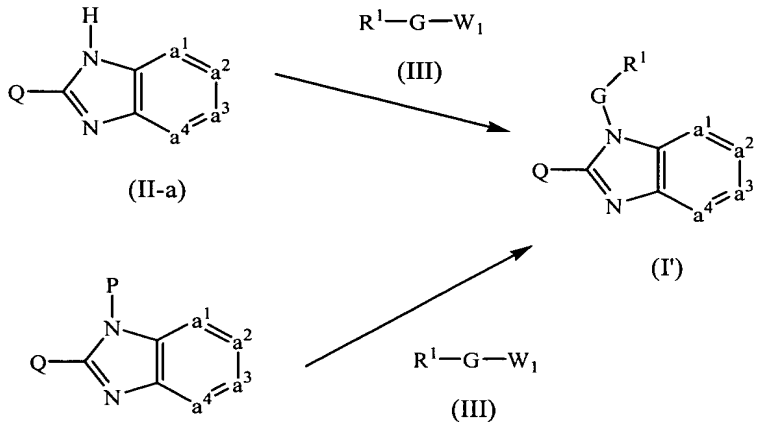
12. ***(cancelled)***

13. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 2 to 4, 6, 8 to 9.

14. A process of preparing a composition as claimed in claim 13, comprising the step of intimately mixing said carrier with said compound.

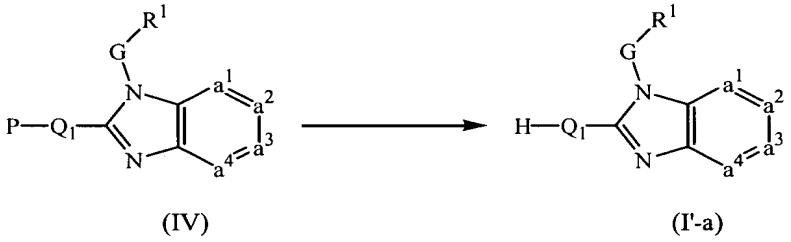
15. A process of preparing a compound as claimed in claim 2, comprising at least one step selected from the group consisting of:

a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III)



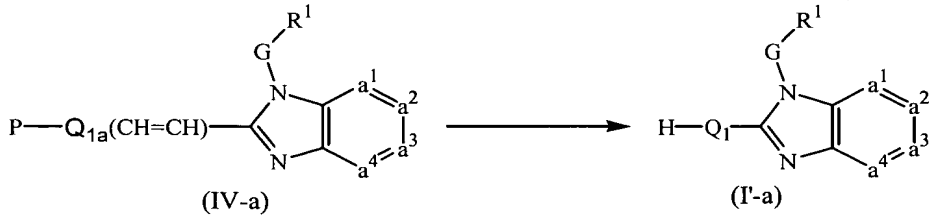
with R^1, G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and W_1 being a leaving group, in the presence of a base and in a reaction-inert solvent;

b) deprotecting an intermediate of formula (IV)



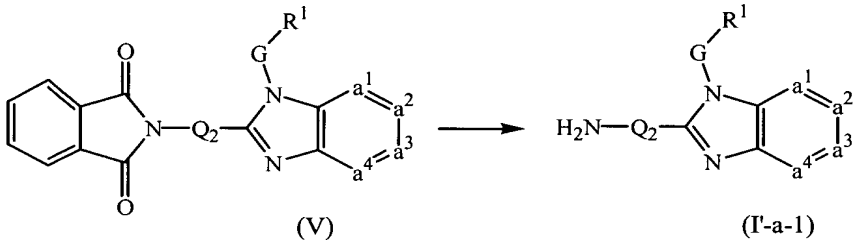
with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, H-Q_1 being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen, and P being a protective group;

c) deprotecting and reducing an intermediate of formula (IV-a)



with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, H-Q_1 being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen, Q_{1a}(CH=CH) being defined as Q_1 provided that Q_1 comprises an unsaturated bond, and P being a protective group;

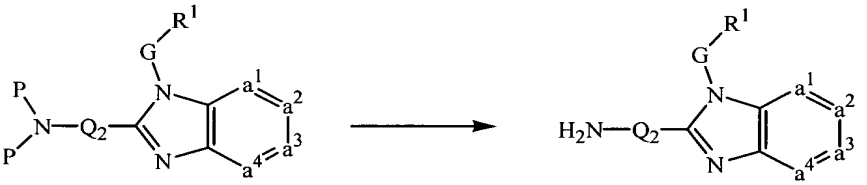
d) deprotecting an intermediate of formula (V)



(V) (I'-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_2 being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen;

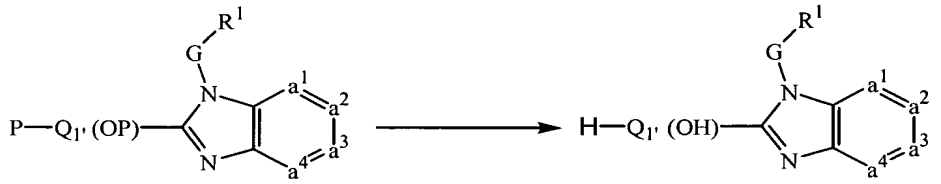
e) deprotecting an intermediate of formula (VI)



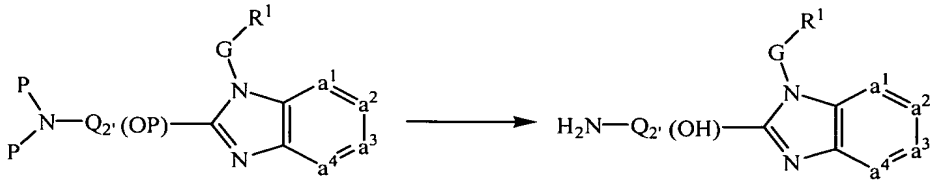
(VI) (I'-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_2 being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and P being a protective group;

f) deprotecting an intermediate of formula (VII) or (VIII)



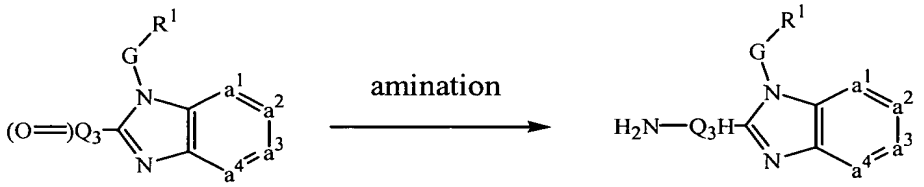
(VII) (I'-a-2)



(VIII) (I'-a-1-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, $H-Q_1$-(OH) being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen and provided that Q comprises a hydroxy moiety, H_2N-Q_2-(OH) being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen and provided that Q comprises a hydroxy moiety, and P being a protective group;

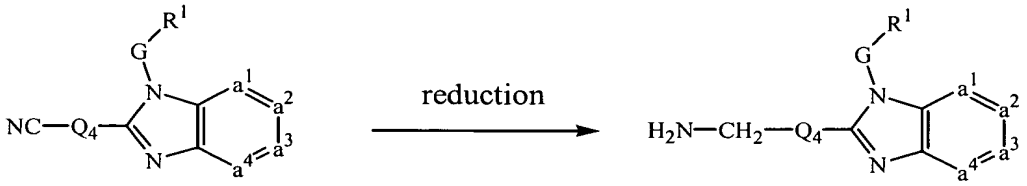
g) amination of an intermediate of formula (IX)



(IX) (I'-a-1-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_3H being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6, or R^2 and R^4 substituents contains at least one hydrogen, in the presence of an amination reagent;

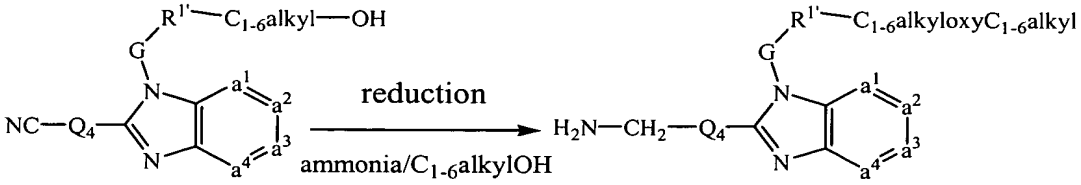
h) reducing an intermediate of formula (X)



(X) (I'-a-1-3)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 2 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a reducing agent;

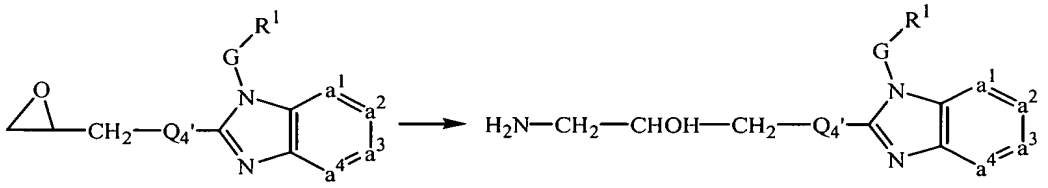
i) reducing an intermediate of formula (X-a)



(X-a) (I'-a-1-3-1)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, $H_2N-CH_2-Q_4$ being defined as Q according to claim 2 provided that Q comprises a $-CH_2-NH_2$ moiety, and $R^{1'}$ being defined as R^1 according to claim 2 provided that it comprises at least one substituent, in the presence of a reducing agent and solvent;

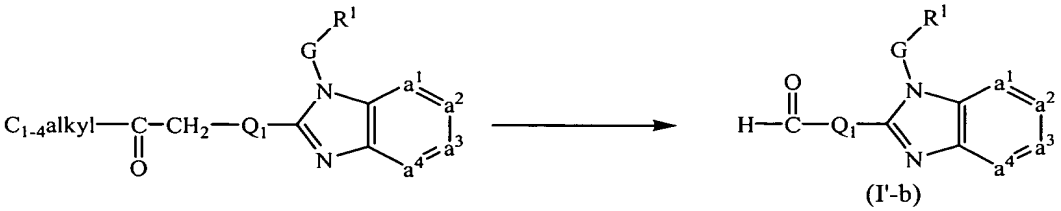
j) amination of an intermediate of formula (XI)



(XI) (I'-a-1-3-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H_2N-CH_2-CHOH-CH_2-Q_4$· being defined as Q according to claim 2 provided that Q comprises a $CH_2-CHOH-CH_2-NH_2$ moiety, in the presence of an amination reagent;

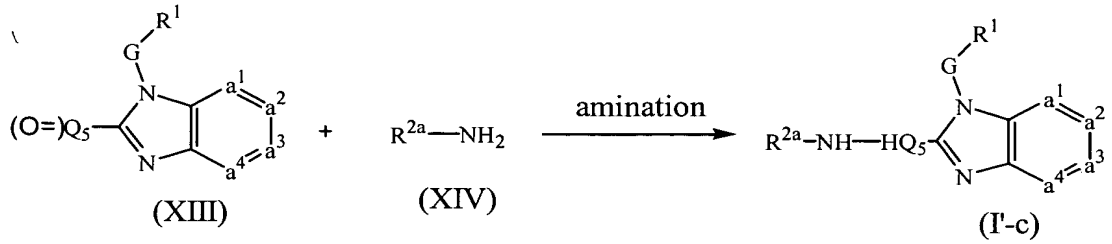
k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia



(XII) (I'-b)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H-C(=O)-Q_1 being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is formyl;

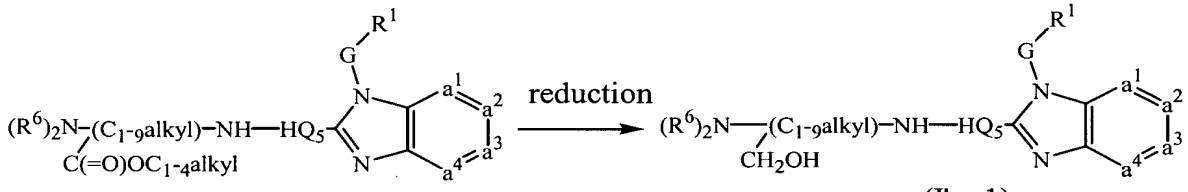
l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)



(XIII) (XIV) (I'-c)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and R^{2a}-NH-HQ_5 being defined as Q according to claim 2 provided that R^2 is other than hydrogen and is represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a reducing agent;

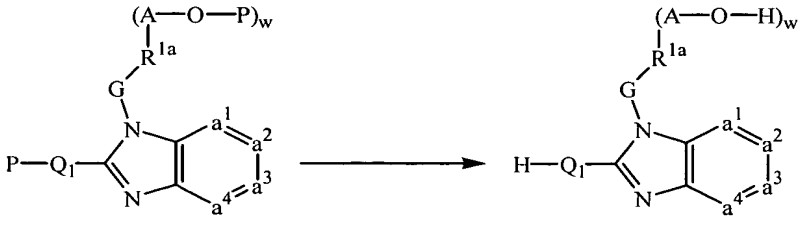
m) reducing an intermediate of formula (XV)



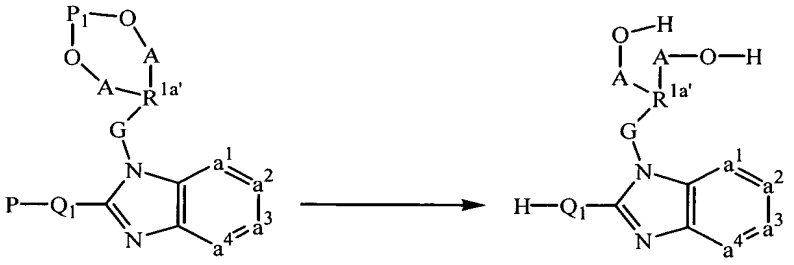
(XV) (I'-c-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $(R^6)_2N$-[$(C_{1-9}$alkyl)CH_2OH]-NH-HQ_5 being defined as Q according to claim 2 provided that R^2 is other than hydrogen and is represented by C_{1-10}alkyl substituted with $N(R_6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a reducing agent;

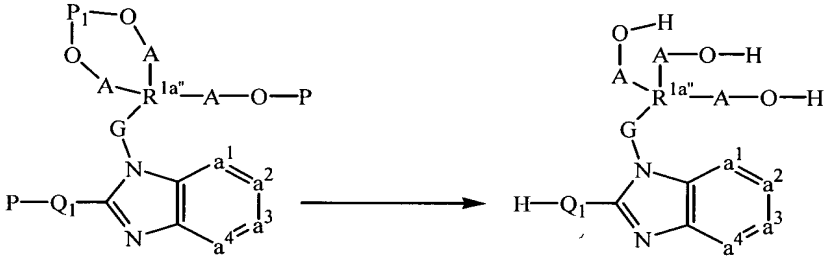
n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b)



(XVI) (I'-d)



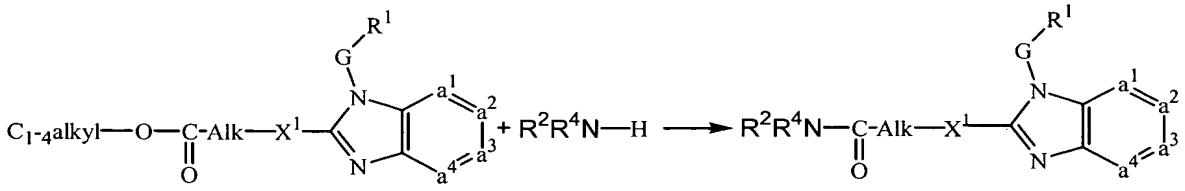
(XVI-a) (I'-d-1)



(XVI-b) (I'-d-2)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H-Q_1 being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen, and R^{1a}-(A-O-H)$_w$, $R^{1a'}$-(A-O-H)$_2$ and $R^{1a''}$-(A-O-H)$_3$ being defined as R^1 according to claim 2 provided that R^1 is substituted with hydroxy, hydroxyC_{1-6}alkyl, or HO(-CH_2-CH_2-O)$_n$-, with w being an integer from 1 to 4 and P or P_1 being a protecting group, with an acid;

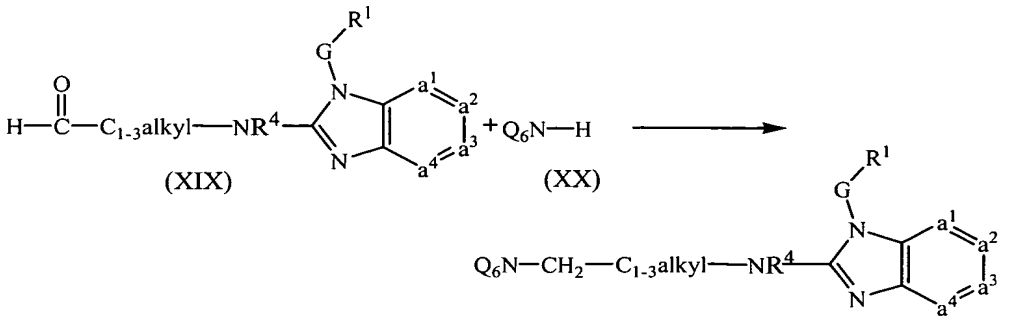
o) amination of an intermediate of formula (XVII)



(XVII) (XVIII) (I'-e)

with R^1, G, $-a^1=a^2-a^3=a^4-$, Alk, X^1 R^2 and R^4 defined as in claim 2, in the presence of an amination agent; and

p) amination of an intermediate of formula (XIX)



(XIX) (XX) (I'-p)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $Q_6N-CH_2-C_{1-3}alkyl-NR^4$ being defined as Q according to claim 2 provided that in the definition of Q, X^2 is $C_{2-4}alkyl-NR^4$, in the presence of an amination agent.

16. ***(cancelled)***

17. ***(cancelled)***

18. The process of claim 15, further comprising the step of converting compound of formula (I') or stereochemically isomeric forms thereof, into a therapeutically active non-toxic acid addition salt by treatment with an acid.

19. The process of claim 15, further comprising the step of converting compound of formula (I') or stereochemically isomeric forms thereof, into a therapeutically active non-toxic base addition salt by treatment with alkali.

20. The process of claim 15, further comprising the step of converting the acid addition salt form of compound of formula (I') or stereochemically isomeric forms thereof, into the free base by treatment with alkali.

21. The process of claim 15, further comprising the step of converting the base addition salt form of compound of formula (I') or stereochemically isomeric forms thereof, into the free acid by treatment with acid.

22. ***(cancelled)***

allergy

1. <immunology> A state of hypersensitivity induced by exposure to a particular antigen (allergen) resulting in harmful immunologic reactions on subsequent exposures, the term is usually used to refer to hypersensitivity to an environmental antigen (atopic allergy or contact dermatitis) or to drug allergy.

The original meaning, now obsolete, included all states of altered immunologic reactivity, immunity as well as hypersensitivity. Gell and Coombs used the term allergic reaction to mean any harmful immunologic reaction causing tissue injury.

2. <study> The medical specialty dealing with diagnosis and treatment of allergic disorders.

(18 Nov 1997)

Previous: allergic salute, allergin, allergised, allergist, allergization, allergosis
Next: allergy and immunology, allergy desensitization, allergy shots

RSV -->

respiratory syncytial virus

<virology> This RNA virus is a member of the Paramyxoviridae family and is a major pathogen in the upper and lower respiratory tract in both infants and younger children.

Respiratory syncytial virus manifestations include bronchiolitis, pneumonia and croup.

Acronym: RSV

(27 Sep 1997)

Previous: respiratory region of tunica mucosa of nose, respiratory scleroma, respiratory sound, respiratory sounds
Next: respiratory syncytial virus, bovine, respiratory syncytial viruses

infection

1. <microbiology> Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication or antigen antibody response. The infection may remain localised, subclinical and temporary if the bodys defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system.

2. An infectious disease.

(18 Nov 1997)

Previous: infarct, infarction, infauna, infaust, infect, infected, infected abortion
Next: infection calculus, infection control, infection control, dental